## REMARKS

Claims 18, 21-25, 28 and 39-58 were pending in the instant application. Claim 18 has been amended. Accordingly, upon entry of the present Amendment, claims 18, 21-25, 28 and 39-58 will be pending in the application, and claims 39-58 remain withdrawn.

Applicants respectfully submit that no new matter has been introduced by the foregoing claim amendments. Support for the claim amendments and the new claims presented herein may be found throughout the originally filed application and claims. Specifically, support for the amendments to claim 18 can be found at least in Figure 1A, as filed, and at least at paragraphs [023]-[025] of the specification as filed.

Amendment and/or cancellation of the claims is not to be construed as acquiescence to any of the objections/rejections set forth in the instant Office Action and was done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims, as originally filed, or similar claims in this or one or more subsequent patent applications.

### *Acknowledgement of Withdrawal of Previous Rejections*

Applicants gratefully acknowledge the withdrawal of the following previous rejections:

The Examiner has withdrawn the rejection of claims 18, 21-25 and 28 Under 35 U.S.C. § 103(a) as being unpatentable over Fischer (U.S. Patent No. 6,939,543) in view of Patti (U.S. Patent No. 6,703,025).

The Examiner has withdrawn the rejection of claims 18, 24, and 28 under 35 U.S.C. § 102(b) as being anticipated by Hunter *et al.* (U.S. Patent No. 4,954,449) in view of Argaman *et al.* (1974).

The Examiner has withdrawn the rejection of claims 18 and 25 under 35 U.S.C. §112, first paragraph.

### *Obviousness-Type Double Patenting*

The Examiner maintained the rejection of claims 18, 21-25 and 28 under the judicially created doctrine of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 7,169,903 (Attorney Docket No. SYNI-008).

The Examiner contends that:

> [t]hough the scope of the allowed claims is not identical to the instant claims, the allowed claims are directed to a genus of compositions that comprise antibodies of the instant claims, the instant claimed being a species of invention encompassed by the allowed genus.

The Examiner further contends that the instant claims encompass "monoclonal antibodies directed to teichoic acids plus additional carbohydrates and proteins depending on the species and include monoclonal antibodies directed to GlcNAc (N-acetylglucosamine) modification and cross react with WTA from other staphylococcal species."

Applicants respectfully disagree. By contrast to the Examiner's assertions the instant claims are directed to a pharmaceutical composition comprising a therapeutically effective amount of a monoclonal antibody or an antigen binding fragment thereof that ***specifically binds to ribitol phosphate wall teichoic acid (WTA) of Figure 1A of S. aureus***, wherein said therapeutically effective amount of said antibody or fragment thereof alleviates or blocks ***nasal colonization*** or infection by *S. aureus* upon administration to a patient.

Conversely, the claims of the '903 patent are directed to 1) compositions comprising a therapeutically effective amount of a monoclonal antibody, or an antigen-binding portion thereof, that ***specifically binds to peptidoglycan (PepG)*** and 2) compositions comprising such anti-PepG antibodies which specifically bind PepG in combination with an antibody, or antigen-binding fragment thereof, that ***specifically binds to lipoteichoic acid (LTA)***.

The pending claims have been limited to antibodies that are ***specific for the ribitol phosphate WTA of S. aureus (as shown in Figure 1A)*** and encompass different subject matter than the '903 patent. The claimed antibodies would not significantly cross-react with peptidoglycan or lipoteichoic acid (LTA). The Examiner has not provided evidence to the contrary. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 18, 21-25 and 28.

***Objection to the Drawings/Claims***

**Figure 1A**

The Examiner has objected to Figure 1A because the descriptors "TagO" and "DltABCD" are not explicitly described in the Brief Description of Figure 1A.

Applicants note that a skilled artisan would understand the clear meaning of the references to "TagO" and "DltABCD" in Figure 1A. Nevertheless, Applicants have amended the Brief Description of Figure 1A to recite "[c]omponents of the structure are further labeled with the genes or operons, such as TagO and DltABCD, which encode compounds involved in the structure's synthesis." The amendment to Figure 1A is supported in the specification, at least in the Brief Description of Figure 1B and at paragraph [0087][1]. Furthermore, support for the recitation of "DltABCD" can be found at least at paragraph [0125] of the specification and in cited reference 68 which describes the dlt operon (Peschel, A. et al. 1999. Inactivation of the dlt operon in Staphylococcus aureus confers sensitivity to defensins, protegrins and other antimicrobial peptides. J. Biol. Chem. 274:8405-8410).

Applicants request favorable reconsideration and withdrawal of this objection.

**Figure 1A**

The Examiner has objected to Figure 1A because the Brief Description of Figure 1A recites "gray boxes," and no gray boxes appear in Figure 1A. Applicants have amended the Brief Description of Figure 1A to recite "depicted in braces" rather than "highlighted with gray boxes." Accordingly, this objection is now moot.

**Figure 4B**

The Examiner has objected to Figure 4B because the Brief Description of Figure 4B recites "gray bars" while the gray bars are not easily distinguishable in the Figure. Applicants note that the data shown in Figure 4B cannot be misunderstood because the bars on the graph are clearly labeled. Notwithstanding the foregoing, Applicants have submitted herewith a replacement drawing for Figure 4B which more clearly distinguishes the gray bars. Applicants respectfully request favorable reconsideration and withdrawal of the objection to Figure 4B.

[1] [0087] provides "...staphylococcal organism deficient in WTA may be constructed by inactivating a staphylococcal gene that produced a biological product that is involved in synthesizing WTA or incorporating WTA into the bacterial cell wall. Such genes include, but are not limited to, the tagO gene."

**Figure 5A**

The Examiner notes that paragraph [038] refers to "gray triangles" "which are only shown in LL-37 figure, while the other two images also have Δ's that are not gray." Upon inspection of the relevant paragraph, Applicants believe that the Examiner was referring to paragraph [035]. Applicants have amended paragraph [035] to remove the word "gray." Accordingly, the objection to Figure 5A is moot.

**Claim 18**

The Examiner has objected to claim 18 for reciting "Figure 1A." Applicants have amended claim 18 to include the relevant portion of Figure 1A, thereby rending this objection moot.

***Rejection of Claims 18, 21-25 and 28 Under 35 U.S.C. § 103(a)***

The Examiner has rejected claims 18, 21-25 and 28 under 35 U.S.C. § 103(a) as being unpatentable over Gotz and Peschel (common inventor, DE19912706) *et al.* in light of English translation, in view of Fischer *et al.* (U.S. Patent No. 6,939,543) in view of Patti *et al.* (U.S. Patent No. 6,703,025).

Specifically, the Examiner is of the opinion that

> Gotz et al teach and show the chemical structure of the ribitol teichoic acid (see De19912706, figure 1, Wandteichonsaure) for Staphylococcus aureus strain Sa113 (same strain as the instant Application, see De 19912706 col. 7, line 45) and antibodies directed thereto (see De 1992706 col. 5, line 62 "spezifischen Antiseren", col. 6, lines 28-30 and lines 17-32, col. 6, lines 56-58 and English machine translation. Gotz et al teach antibodies in antiserum... that specifically bind to ribitol teichoic acid of Staphylococcus aureus strain Sa113....
>
> Gotz et al teach active agents that reduce or inhibit Gram Positive bacterial/infection and biofilm formation(see at least claims 19-26), formulation of compositions for administration, suggests pharmaceutical compositions and polyclonal antibodies directed to the ribitol wall teichoic acid of Staphylococcus aureus but differs from the instantly claimed invention by failing to show antibodies in the compositions to be monoclonal antibody compositions formulated as pharmaceutical compositions....

The Examiner concluded that it would have been obvious to modify the compositions of Gotz *et al.* as taught by Fischer *et al* (teaching the importance of polyclonal, monoclonal and other antibodies) and Patti *et al.* (teaching "the production of antibodies to glycerol or ribitol phosphate"). Applicants respectfully traverse the foregoing rejection.

Applicants respectfully traverse this rejection on the grounds that the Examiner has failed to establish a *prima facie* case of obviousness since none of Gotz, Fischer, or Patti, alone or in combination, teach or suggest the claimed invention and further fail to provide the necessary motivation or reasonable expectation of success for the ordinarily skilled artisan to arrive at the presently claimed invention.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to apply a flexible teaching, suggestion, or motivation test to combine known elements in order to show that the combination is obvious. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Importantly, the *KSR* Court noted that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some

rational underpinning to support the legal conclusion of obviousness." (*In re Kahn*, 441 F.3d 911,988 (CA Fed. 2006) cited with approval in KSR).

The test for *prima facie* obviousness is consistent with the legal principles enunciated in KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." Id. (quoting KSR, 127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. KSR, 127 S. Ct. at 1731. The KSR Court upheld the secondary considerations of non-obviousness, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." Id. Although the prior art reference, or references when combined, need not teach or suggest all of the claim limitations, a *reason* must be given why the differences between the prior art and the claimed limitation would have been obvious to one of skill in the art (see Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, Federal Register, Vol. 72, No. 195).

The claims, as amended, are directed to a ***pharmaceutical composition*** comprising a therapeutically effective amount of a monoclonal antibody or an antigen binding fragment thereof that ***specifically binds to a ribitol phosphate wall teichoic acid (WTA) of S. aureus and a pharmaceutically acceptable carrier***, wherein said therapeutically effective amount of said antibody or fragment thereof alleviates or blocks ***nasal colonization*** or infection by *S. aureus* upon administration to a patient.

Contrary to the Examiner's suggestion, the "active ingredients" referred to by Gotz *et al.* are ***not antibodies or antiserums***. The "active ingredients" are peptides or proteins which are involved in the incorporation of D-alanine into teichoic acid.[2] These active ingredients are used to increases the sensitivity of the microorganisms to antimicrobial substances.[3] Accordingly, Gotz *et al.* do not teach the administration of antibodies that ***specifically bind to a ribitol phosphate wall teichoic acid*** (WTA) of *S. aureus* in a ***therapeutically effective amount*** to ***alleviate or block nasal colonization or infection*** by *S. aureus* as presently claimed.

The Examiner further notes that antiserums are disclosed by Gotz *et al.* Nevertheless, the antiserums employed by Gotz *et al.* are hypothetical and merely suggested as diagnostic tools to test for the presence or effectiveness of the above mentioned "active ingredients." Indeed the term "antiseren" is mentioned only 4 times in Gotz *et al.*:

- At col 5, lines 53-55 and col 5, lines 59-61 several types of compounds including dyes, fluorescent molecules, radioactive isotopes, and antiserums are listed as substances which may be used to detect bacteria, biofilm formation, or the binding ability of "teichonsauren" at surfaces.[4] This paragraph does not mention ribitol phosphate wall teichoic acid.
- At col 6, lines 26-32 "antiseren" is mentioned twice in the context of detecting the effectiveness of active ingredients. A more complete excerpt surrounding the sentence chosen by the examiner reads as follows (English machine translation):

[2] From the English machine translation of Gotz *et al.* "The active ingredient according to invention preferably sets with peptides/proteins, which at the incorporation of D-alanine in Teichonsauren of Gram positive bacteria involved is." - originally col. 2, paragraph 3, beginning at line 18 of Goetz et al.

[3] From the English machine translation of Gotz *et al.*: "The use of an active ingredient according to invention leads to the fact that the microorganisms, which are to be fought develop a sensitivity or higher sensitivity opposite antimicrobial substances." – originally col. 2, paragraph 4, beginning at line 46 of Goetz *et al.*

[4] Col 5, line 55 (English machine translation: " The proof of the bacteria, the Schleimsubstanz or the schleimbildenden substances can take place with dyes, groups of fluorescences, radioactive isotopes or specific antiserums."); Col 5, lines 56-61 (English machine translation: "Favourable also the determination of binding ability of Teichonsauren at surfaces is with addition, potential active ingredients which can be tested. The proof can take place via mark of the Teichonsauren with radioactive isotopes, dyes or groups of fluorescences or become with specific antiserums performed."

> The measurement of the alanine installation can take place direct at the Teichonsauren after treatment of the microorganisms with a potential active ingredient, or it can become the connection of D-alanine to enzymes of the alanine installation and/or the conversion of D-alanine by enzymes of the D-Alanineinbaus certain. The proof of the D-alanine or the enzymes can take place with radioactive isotopes, with coloring material or groups of fluorescences, or with antiserums, which recognize specific alanine-substituted or non-substituted Teichonsauren. Also antiserums used cannot become, which recognize specific enzymes, the alanine bound or bound to have.

Though the machine translation is not perfect, it is clear that any antiserum mentioned is employed only as an assay to detect the effects of the "active ingredient" on D-alanine substitution. Moreover, the antiserums are not formulated as ***pharmaceutical compositions*** comprising a ***pharmaceutically acceptable carriers***, as presently claimed. As Gotz *et al.* merely suggested the hypothetical use of antiserum as a reagent to assay for the presence of another agent (*i.e.*, an "active ingredient"), one of skill in the art would not have been motivated to make or use antibodies specific for WTA of *S. aureus* to treat infection based on the teaching of Gotz *et al.*

It is well understood that, to establish obviousness, a prior art reference must teach or suggest the claimed invention. As there is no teaching or suggestion in Gotz *et al.* as to the importance of WTA in the pathology of nasal infection and colonization by *S. aureus*, a skilled artisan would not have been motivated to make the presently claimed antibodies. In fact, it was not until applicants generated and characterized the Δ*tagO* WTA deficient mutant (see Examples 1-3 of the Specification) that the criticality of WTA for nasal colonization (see Example 4) by *S. aureus* was understood. This unexpected finding led Applicants to develop methods to treat and prevent nasal colonization by *S. aureus, e.g.*, the presently claimed antibodies (see Example 5). By contrast, the disclosure of Gotz *et al.* would not have motivated the skilled artisan to make antibodies directed to ribitol phosphate WTA of *S. aureus*, let alone antibodies which are effective to alleviate or block nasal colonization or infection.

It also understood that, to establish obviousness, a prior art reference must enable the claimed invention. In re Kumar, 418 F.3d 1361, 1368 (Fed. Cir. 2005). "Rebuttal evidence may show, for example, that the claimed invention achieved unexpected results relative to the prior art, In re Geisler, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997) ..... or that the prior art did not enable one skilled in the art to produce the now-claimed invention, In re Payne, 606 F.2d 303, 314-15 (CCPA 1979)." In re Kumar, 418 F.3d 1361, 1368 (Fed. Cir. 2005).

Applicants respectfully note that the Examiner has mischaracterized the antiserum of Gotz *et al.* as a "known product"[5] when in fact Gotz *et al.* does not teach or suggest antibodies specific for ribitol phosphate wall teichoic acid as therapeutic agents, nor does it provide any examples of, or teach methods to make, therapeutic antibodies specific for ribitol phosphate wall teichoic acid of *S. aureus*. Indeed, Gotz *et al.* adds nothing to the teachings of Fisher *et al.* and Patti *et al.* Accordingly, Gotz *et al.,* either alone or in combination with Fisher and Patti, is not enabling for the presently claimed invention.

As set forth in Applicants' response of October 3, 2008, neither Fischer *et al.* nor Patti *et al.* teach or suggest antibodies which specifically bind the ribitol teichoic acid of *S. aureus* as set forth in the instant claims, nor do the references teach or suggest the presently claimed pharmaceutical compositions. Therefore, Fisher and Patti do not make up for the deficiencies of Gotz. Moreover, a skilled artisan would not have been motivated to combine the cited references. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." M.P.E.P. 2143.01, III, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007). One of skill in the art would not have been motivated to formulate the "antiserums" recited by Gotz *et al.* into a pharmaceutical composition, nor would one of skill in the art predict based on Gotz that antibodies to WTA of S. aureus could be therapeutically useful. Indeed, there is no evidence that the antiserums of Gotz, even if they had been produced, would have had the claimed characteristics.

Accordingly, Applicants respectfully request that the rejection of claims 18, 21-25 and 28 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

[5] Page 11 of the instant Office Action.

## SUMMARY

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

In addition, Applicants include herewith authorization to charge fees associated with new claims and the extension of time with which to respond, to Deposit Account No. 12-0080, under Order No. SYNI-007RCE2. The Director is also hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 12-0080, under Order No. SYNI-007RCE2.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: June 30, 2009

Respectfully submitted,
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Attachments:
Replacement Sheet for Figure 4B